Janssen Research & Development

Statistical Analysis Plan

A Safety and Efficacy Study of JNJ-68284528, (ciltacabtagene autoleucel) Out-of-Specification (OOS) for Commercial Release in Patients with Multiple Myeloma

Protocol 68284528MMY2005; Phase 2

JNJ-68284528 (ciltacabtagene autoleucel)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Initial release

1. INTRODUCTION

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of cilta-cel OOS	• Overall Response of partial response or better (i.e., ORR), as defined by the International Myeloma Working Group (IMWG) response criteria and assessed by the investigator. Time frame: Screening Phase through End of Study (EOS) (Month 24 after cilta-cel OOS infusion/Early withdrawal).
Secondary	
• To assess the safety of cilta-cel OOS	• Incidence and severity of treatment-emergent adverse events, serious adverse events, abnormalities in safety (laboratory assessments), vital signs, and physical examinations
• To further characterize the efficacy of cilta-cel OOS	• Partial Response (PR)/very good partial response (VGPR)/complete response (CR)/stringent complete response (sCR) rate and clinical benefit rate (CBR=ORR [sCR+CR+VGPR+PR]+MR [minimal response]), as defined by the IMWG response criteria, duration of response (DOR), progression-free survival (PFS), overall survival (OS) and minimal residual disease (MRD)-negative rate.
• To determine whether replication competent lentivirus is present in participants that receive cilta-cel OOS	• Presence of replication competent lentivirus
Exploratory	
• To characterize the pharmacokinetics and pharmacodynamics of cilta-cel OOS	• Biomarkers including baseline expression of BCMA in MM cells, depletion of BCMA expressing cells, systemic cytokine concentrations, and CAR-T PK parameters such as expansion and persistence via monitoring CAR-T positive cell counts, and CAR transgene levels
• To assess the immunogenicity of cilta-cel OOS	• Presence of anti-cilta-cel OOS antibodies.

Abbreviations: BCMA=B-cell maturation antigen; CAR-T=Chimeric antigen receptor-T cells; CBR=clinical benefit rate; CR=complete response; DOR=duration of response; EOS=End of Study; IMWG=International Myeloma Working Group; MM=multiple myeloma; MRD=minimal residue disease; MR=minimal response; OOS=Out-of-Specifications; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

1.2. Study Design

This is a Phase 2, open-label, single-arm, multicenter study of cilta-cel OOS administered to adult participants (≥ 18 years) with multiple myeloma whose final manufactured cilta-cel does not meet the commercial release specifications (cilta-cel OOS) and whose expected benefit/risk profiles for cilta-cel OOS are assessed as favorable by the sponsor. The aim of the study is to evaluate the safety and efficacy of cilta-cel OOS. It was planned to enroll at least 20 participants. An overview of the trial design can be found in Figure 1 of the Protocol.

Safety and efficacy of participants who received cilta-cel OOS will be evaluated at the periodic Data Review Committee (DRC) meetings. Initially, data will be reviewed by a commissioned DRC after every 10 participants have been treated and followed for at least 3 months.

Eligible participants will be administered a lymphodepleting chemotherapy of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days per United States prescribing information (USPI) or locally approved label. Cilta-cel OOS will be administered at a total target dose of $0.75x10^6$ CAR-positive viable T cells/kg (range: 0.5 to $1.0x10^6$ CAR-positive viable T cells/kg) or per exceptional release criteria determined alternative dose, 5 to 7 days after the start of the lymphodepleting chemotherapy (Section 4.1 of Protocol).

Efficacy evaluations include myeloma protein measurements and imaging as indicated for enrolled participants to evaluate response and disease progression. Disease status will be evaluated by the investigator according to clinical judgement guided by the International Myeloma Working Group (IMWG) consensus recommendations[4] for multiple myeloma treatment response criteria (Section 10.10, Appendix 10 of Protocol).

Safety of cilta-cel OOS infusion will be assessed by adverse events, laboratory test results, vital sign measurements, physical examination findings, handwriting assessments, assessment of Immune-Effector Cell-associated Encephalopathy (ICE) Tool scores, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade.

Following the cilta-cel OOS infusion, participants were to be followed for 2 years in this study to assess response, DOR, PFS, OS and safety. All participants who received citla-cel OOS will continue to be monitored for long-term safety under a separate long-term follow-up study (68284528MMY4002) for up to 15 years after the infusion of cilta-cel OOS.

It was decided by Janssen to prematurely discontinue the study. This decision was made on 19 April 2023. Participants will remain in this study until a minimum of Day 184 visit. Participants treated with cilta-cel OOS will be offered participation in the long term follow-up study, 68284528MMY4002. Sites were instructed to ensure all participants were offered participation in 68284528MMY4002 by the time the last patient infused with cilta-cel OOS in the study reaches Day 184.

2. STATISTICAL HYPOTHESES

Since there is no statistical hypothesis for this study, no formal statistical hypothesis testing is planned.

3. SAMPLE SIZE DETERMINATION

Sample size for this study is not based on statistical consideration. Based on the manufacturing experience with the study 68284528MMY2001, at least 20 participants were anticipated to enroll in the study.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
All Consented Analysis Set	The all consented analysis set includes all participants who signed the informed consent for the study
All Treated Analysis Set	The all treated analysis set includes all participants who received study intervention (cilta-cel OOS).
Response-evaluable Analysis Set	The response-evaluable analysis set includes all participants who received cilta-cel OOS, had measurable disease at baseline, and had at least one post-baseline efficacy assessment
Pharmacokinetics Analysis Set	The PK analysis set is defined as all participants who received a cilta-cel OOS infusion and have at least 1 post-dose pharmacokinetic sample evaluation available.
Immunogenicity Analysis Set	The immunogenicity analysis set is defined as all participants who received a cilta-cel OOS infusion and have at least 1 post-dose immunogenicity sample evaluation available.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Visit Windows

Unless otherwise specified, data to be analyzed or listed over time will be presented by scheduled visit and time point (as appropriate) that are recorded in the electronic case report form (eCRF).

For safety laboratory (chemistry, hematology, coagulation) and vital sign parameters besides temperature, the following visit window rule will be applied for summaries of parameter values by visit/time point: for each scheduled visit/timepoint and parameter, if there are multiple non-missing records per participant, the record with latest date/time will be selected for summary. For temperature, if a participant has multiple non-missing records per scheduled visit/timepoint, following this selection order to choose a unique record: (1) choose a unique record for summary by selecting value from clinic visit over diary entries, and (2) choose the record with the latest date/time. For RCL, the following visit window will be used:

- Pre-dose of cilta-cel OOS infusion (target study day = 1): study day=1
- 3 months after cilta-cel OOS infusion (target study day = 91): $2 \leq$ study day ≤ 137

- 6 months after cilta-cel OOS infusion (target study day = 183): 138 ≤ study day ≤ 274
- 12 months after cilta-cel OOS infusion (target study day = 365): 275 ≤ study day ≤ 457

If there are multiple RCL results within a visit window per participant, choose the result closes to the target day and if there are still multiple results after this step, choose the record with the last date.

5.1.2. Pooling Algorithm for Analysis Centers

Data from all study centers will be pooled for analysis purpose.

5.1.3. Study Intervention

Study intervention refers to cilta-cel OOS.

5.1.4. Study Day and Relative Day

Study Day 1 refers to the start date of the first infusion of cilta-cel OOS.

Study day or relative day for a visit or assessment/event is defined as:

- visit date - date of Study Day 1 +1, if visit date ≥ date of Study Day 1 (i.e., on or after cilta-cel OOS infusion)
- visit date - date of Study Day 1, if visit date < date of Study Day 1 (i.e., prior to cilta-cel OOS infusion)

5.1.5. Baseline

The baseline value is defined as the closest non-missing value before the first infusion of cilta-cel OOS (including time if time is available), with exception of parameters associated with disease-related efficacy assessment (such as SPEP, UPEP, SIFE, UIFE, kappa, lambda, kappa/lambda ratio) for which the baseline value is defined as the latest non-missing value on and before cilta-cel OOS infusion (excluding time). For parameters that are not associated with disease-related efficacy assessment, if the assessment date is the same as the first infusion date of cilta-cel OOS but the time is missing, the assessment will be considered baseline if the Schedule of Activities (Table 1 of Protocol) states that the corresponding test is to be conducted pre-dose.

5.1.6. Unique Efficacy Laboratory Values

In general, in instances when there are multiple records at a given visit date for laboratory parameters associated with disease assessment, the following rules will be applied to select the unique laboratory values for analysis:

- For SPEP, UPEP, FLC, serum and urine immunofixation, immunoglobulin (IgA, IgD, IgE, IgG, IgM, etc.): (a) if multiple records from both central and local laboratory are available, central laboratory value always takes precedence over local laboratory values; b) if multiple records selected after step (a), select records with specimen condition by priority of frozen over refrigerated over ambient/room temperature ; c) if multiple records selected

after step (b), select the scheduled visit record; d) if multiple records selected after step (c), select the record with the largest visit number/sequence number.

- For percent plasma cells (by biopsy/aspirate), choose the largest value of percent plasma cells

5.1.7. Imputation Rules for Missing Date/Time of Onset/Resolution

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purposes, missing or partial dates in AE (AE onset date, AE end date), concomitant therapies (start date, end date), multiple myeloma diagnosis date, prior multiple myeloma therapies (start date, end date), progressive disease date on prior multiple myeloma therapy, and start date of subsequent antimyeloma therapy will be imputed as specified below.

5.1.7.1. Adverse Event Start/End Date

If the start date of an AE is missing completely or partially, the following imputation rules will be used:

- When month and year are present and the day is missing: if the AE onset month and year are the same as the month and year of first dosing date of study intervention (cilta-cel OOS), the day of the AE start date is imputed to the day of first dosing or the day-component of the AE end date (possibly imputed), whichever is earlier; if the onset month and year are not the same as the month and year of the initial dose of study intervention, the day of the AE start date is imputed to the first day of the month.
- When only onset year is present: if AE end date is available and is prior to first dosing date of study intervention, the day and month of AE end date are used for imputation; otherwise, if the onset year is the same as the year of first dosing date of study intervention, impute to the date of first dosing of study intervention. If the onset year is different from the year of first dosing of study intervention, the 1st of January is imputed.
- If the onset date is completely missing, the earlier one of the initial dosing date of the study intervention and the AE end date is imputed as the onset date.

If the end date of an AE is missing completely or partially, the following imputation rules will be used:

- If month and year are present and the day of the month is missing, the last day of the month is used for imputation.
- If only a year is present, the 31st of December is used for imputation.
- If the imputed date is later than the date of death (if available) after imputation, the date of death will be used as the imputed date.
- If the year of AE end date is missing, no imputation will be applied.

5.1.7.2. Concomitant Medication Start/End Date

In case of partially missing dates, the imputation will be done as follows:

- If the date is completely missing or year is missing, no imputation will be performed.
- Otherwise, the following rules will be applied to impute partially missing dates (start date, end date). If only the day is missing, the 15th day of the month will be used. If both the day and month are missing, the 30th of June will be used.

If the imputed start date is after end date, then re-impute the start date to equal to end date. If the imputed end date is before the start date, then re-impute the end date to equal the start date. If the medication was taken prior to study start, and the imputed start date is after initial dosing date of study intervention, further adjust the imputed start date as one day prior to initial dosing date; if the medication was taken after study start, and the imputed start date is prior to initial dosing date of study intervention, further adjust the imputed start date as initial dosing date.

Also, further adjust the imputed medication end date so that it is on or after initial dosing date (as long as it is in line with the partial date information).

5.1.7.3. Multiple Myeloma Diagnosis Date

For partial date of initial multiple myeloma diagnosis, the following imputation rules will be applied:

- If only day is missing,
    - if the month and year of the start of the 1st line of prior multiple myeloma therapy are the same as the year and month of diagnosis, and the day of the start of the 1st line of prior multiple myeloma therapy is available, impute day to the day of the start of the 1st line of prior multiple myeloma therapy
    - otherwise, impute day to 15
    - if the imputed diagnosis date is on or after the date the informed consent is signed, further adjust the imputed diagnosis date to one day prior to the date the informed consent is signed
- If both month and day are missing,
    - if the year of diagnosis is the same as the year of the start of the 1st line of prior multiple myeloma therapy, and month information is available for the start of the 1st line of prior multiple myeloma therapy
        - impute month with the month of start of 1st line of prior multiple myeloma therapy
        - if the day of start of 1st line of prior multiple myeloma therapy is available, impute diagnosis day with the day of start of 1st line of prior multiple myeloma therapy; otherwise, impute diagnosis day with 15
    - otherwise, impute with June 30
    - if the imputed diagnosis date is on or after the date the informed consent is signed, further adjust the imputed diagnosis date to one day prior to the date the informed consent is signed
- If year is missing, no imputation will be applied.

5.1.7.4. Prior Multiple Myeloma Therapy Start/End Date

For partially missing prior multiple myeloma therapy start/end dates, the following imputation rules will be applied. If the date is completely missing or year is missing, no imputation will be performed.

- If only the day is missing, the 15th day of the month will be used.
- If both the day and month are missing, the 30th of June will be used.

If the imputed start/end date is after initial dosing date of study intervention, further adjust the imputed start/end date as the day prior to initial dosing date.

5.1.7.5. Progressive Disease Date on Prior Multiple Myeloma Therapy

For partially missing or completely missing progressive disease date on prior multiple myeloma therapy, the following imputation rules will be applied. Partially missing prior multiple myeloma therapy start/end dates will be imputed before imputing partially missing or completely missing progressive disease date.

- If only the day is missing,
    - if the month and the year are the same as the month and the year of prior multiple myeloma therapy start date, then the day of prior multiple myeloma therapy start date will be used.
    - otherwise, the 15th of the month will be used
- If both the day and month are missing,
    - if the year is the same as the year of prior multiple myeloma therapy start date, then the month and day of prior multiple myeloma therapy start date will be used
    - otherwise, the 30th of June will be used
- If progressive date is completely missing but participant progressed on the prior multiple myeloma line, impute to the latest end date of the medications in the prior line. If progressive date is completely missing but it is unknown whether the participant progressed on the prior line, progressive date will not be imputed

If the imputed progressive disease date is before the prior multiple myeloma therapy start date, further adjust the imputed progressive disease date as the start date of the prior multiple myeloma therapy.

5.1.7.6. Subsequent Antimyeloma Therapy Start Date

If start date is completely missing or year of start date is missing, no imputation will be performed.

If both the month and day components are missing, the following steps apply:

- If the year is the same as the year of study intervention's infusion date or the year of the first post-baseline progressive disease date as assessed by the investigator (recorded in disease progression CRF page), then the month and day of study intervention's infusion date + 1 day

or the month and day of the first post-baseline progressive disease date + 1 day will be used, whichever is later.

- Otherwise, the 30th of June or the stop date of subsequent antimyeloma therapy, whichever is earlier will be used.

If only the day component is missing, the following steps apply:

- If the month and year of the start date are the same as the month and year of the study intervention's infusion date or the month and year of the first post-baseline progressive disease date as assessed by the investigator, then the day of study intervention's end date + 1 day or the day of the first post-baseline progressive disease date + 1 day will be used, whichever is later.
- Otherwise, the first day of the month is imputed.

If the imputed start date of subsequent antimyeloma therapy is after the stop date of subsequent therapy, further adjust the imputed start date of subsequent antimyeloma therapy as the stop date of subsequent therapy.

No imputation will be applied for missing or partial subsequent antimyeloma therapy end date.

5.1.7.7. Death Date

For participants reported as dead, if the recorded death date is partial, impute as follows:

If only the death day is missing:

- If the month and year of the date the participant is last known alive is the same as the year and month of the death date, impute the death date to last known alive date + 1 day
- Otherwise, impute to the first day of the month

If death date is completely missing or if the month or year of death date is missing, no imputation will be done.

5.1.8. Other General Definition

5.1.8.1. Measurable Disease of Multiple Myeloma and Measurable Type

Measurable disease at baseline is defined by any of the following:

- Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
- Light chain multiple myeloma without measurable disease in the serum or the urine: Serum involved free light chain (FLC) ≥10 mg/dL and abnormal serum FLC ratio.

If a participant meets the criteria for serum M-protein, the measurable disease type is serum; otherwise, if a participant meets the criteria for urine M-protein, the measurable disease type is urine; otherwise, if a participant meets the criteria for FLC, the measurable disease type is FLC. If a participant meets both of the criteria for serum M-protein and urine M-protein, then the measurable disease type is "serum and urine".

5.1.8.2. Type of Multiple Myeloma at Baseline

Type of myeloma at baseline for a participant is determined by baseline measured serum heavy chain or serum FLC or urine FLC. Serum heavy chain refers to serum immunoglobin of IgG, IgA, IgM, IgD, or IgE. Serum and urine FLC refer to kappa or lambda type.

A participant will be classified as IgG type of myeloma if any reported result contains serum heavy chain 'IgG' regardless of FLC reported, similarly for IgA, IgM, IgD and IgE type. A participant will be classified as the light chain type of myeloma if any reported result is either 'Lambda light chains' or 'Kappa light chains' but without heavy chain reported. A participant will be reported as 'biclonal' if distinct test results contain different heavy chain values or different FLC values. A participant will be classified as 'Negative immunofixation' if the reported result is 'Not Detected' with no serum heavy chain, serum light chain or urine light chain reported.

5.1.8.3. End of Follow-up and Duration of Follow-up

For participants who died, the end of the follow-up is the date of death. Otherwise, the end of follow-up is defined as the maximum date of the following study evaluations: labs (hematology, chemistry, coagulation, immunology), adverse events, vital signs, ECOG performance status, bone marrow cytogenetics, lytic bone lesions, extra-medullary plasmacytomas, study drug administration, echocardiogram/MUGA, pre-infusion medications, post-infusion medications, concomitant medications, subsequent therapy, medical encounters, clinical events/disease response per investigator, and date of last known to be alive.

Duration of follow-up (in months) = (date of end of follow-up – start date of cilta-cel OOS infusion + 1) /(365.25/12).

5.1.9. Data Handling Rules for Efficacy Analyses

There is no imputation planned for missing efficacy endpoint values.

5.1.10. Level of Significance

Unless specified otherwise, reported confidence intervals (CIs) will be 2-sided 95% CIs. As there is no formal statistical hypothesis testing, the level of significance is not applicable and reported 95% CIs are not for hypothesis testing purpose.

5.2. Participant Dispositions

The number of participants in the following disposition categories will be summarized for the all treated analysis set:

- Participants who discontinued from the study
- Reasons for discontinuation from the study

A listing of participants' study disposition will be provided for the all treated analysis set. A listing of participants who received lymphodepleting chemotherapy but did not receive cilta-cel OOS may be provided.

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The primary endpoint is Overall Response Rate (ORR), defined as the proportion of participants who achieve a PR or better according to the IMWG response criteria[4], as assessed by computerized algorithm and by the investigator.

5.3.2. Estimand

Primary Trial Objective: to evaluate the efficacy of cilta-cel OOS in adult participants with multiple myeloma

Estimand Scientific Question of Interest: What is the proportion of participants considered to have benefited from cilta-cel OOS?

Study treatment: a sequence of lymphodepleting chemotherapy (cyclophosphamide and fludarabine) and cilta-cel OOS infusion

Population: adult participants with multiple myeloma who met study inclusion/exclusion criteria, and received cilta-cel OOS

Variable: Overall response rate (ORR), defined as the proportion of participants in the all treated analysis set who have a best response of PR or better according to the International Myeloma Working Group (IMWG) response criteria. Participants with no post-baseline response evaluation data will be considered as non-responders. Disease assessment after the start of subsequent therapy will not be considered in deriving the ORR.

Summary measure (Population-level summary): proportion and 95% CI of the proportion

Intercurrent events and their corresponding strategies:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Start of subsequent antimyeloma therapy	**While on Treatment Strategy**: disease assessment after the start of subsequent therapy will not be considered in deriving ORR.

5.3.3. Analysis Methods

The ORR per computerized algorithm and per investigator assessment (count and percentage) and its 2-sided 95% Clopper-Pearson exact CI will be presented for the all treated analysis set.

Similar analyses for ORR will be conducted for the response-evaluable analysis set.

A listing of disease response will be provided for the all treated analysis set. The listing will include the following for both response per computerized algorithm and per investigator assessment: first confirmed response and date (study day), best confirmed response and the date (study day) when

this response was first achieved, and first confirmed progressive disease date and study day (if applicable), and a flag for participants in the response-evaluable analysis set.

5.4. Secondary Endpoint(s) Analysis

The secondary efficacy endpoints include VGPR or better rate, CR or better rate, stringent complete response (sCR) rate, clinical benefit rate (CBR=ORR + MR (minimal response)), duration of response (DOR), minimal residual disease (MRD)-negative rate, progression-free survival (PFS), and overall survival (OS).

5.4.1. Other Categories of Best Responses

5.4.1.1. Definition

VGPR or better rate is defined as the proportion of participants who achieve a best response of sCR, CR, or VGPR according to the IMWG response criteria[4]. Similarly, CR or better rate is defined as the proportion of participants who achieve a best response of sCR or CR according to the IMWG response criteria[4]. Clinical benefit rate is defined as the proportion of participants who achieve a best response of MR or better (including sCR, CR, VGPR, PR, and MR).

Participants with no post-baseline response evaluation data will be considered as not achieving these response categories. Disease response assessments after the start of subsequent therapy will not be considered in deriving these endpoints.

5.4.1.2. Analysis Methods

For each category, VGPR or better, CR or better, and clinical benefit rate, counts and percentages and the two-sided 95% Clopper-Pearson exact CIs for the percentages will be presented for the all treated analysis set. Similar statistics will be provided for each best response category (sCR, CR, VGPR, PR, MR, SD, not evaluable (NE), PD) for the all treated analysis set. This analysis will also be performed for the response-evaluable analysis set.

These analyses will be performed for responses based on investigator assessment and based on computerized algorithm assessment according to IMWG criteria.

5.4.2. Minimal Residual Disease (MRD)-Negative Rate

5.4.2.1. Definition

MRD-negative rate is defined as the proportion of participants who have negative MRD by bone marrow aspirate at any timepoint after administration of cilta-cel OOS and before disease progression or start of subsequent anti-myeloma therapy. For the derivation of MRD negative rate, minimal residual disease positive participants include participants for whom all tested samples were found to be MRD positive or ambiguous, and participants with missing or unevaluable MRD status.

For this study, the threshold value of 10^{-5} will be used for the primary MRD negativity analysis. Other threshold values (10^{-4} and 10^{-6}) will also be explored.

5.4.2.2. Analysis Methods

The MRD-negative rate (at 10^{-5}) and its two-sided 95% Clopper-Pearson exact CI will be presented for the following analysis sets: (1) all treated analysis set, (2) the all treated analysis set with MRD-evaluable sample at 10^{-5} (defined as participants in the all treated analysis set whose samples passed calibration and QC and included sufficient cells for evaluation at the testing threshold of 10^{-5}).

Summary of diagnostic or baseline bone marrow aspirate sample calibration rate will be provided. Participants whose MRD samples failed calibration or QC will be listed. Reasons for missing or unevaluable MRD status, if recorded, may be listed for the all treated analysis set.

In addition, MRD-negative rate at 10^{-4} and 10^{-6} and corresponding 95% Clopper-Pearson exact CIs will be provided for the all treated analysis set with MRD-evaluable sample at 10^{-4} and 10^{-6} respectively.

5.4.3. Duration of Response

5.4.3.1. Definition

Duration of response (DOR) will be calculated among responders (with a PR or better) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria[4], or death due to any cause, whichever occurs first. Participants who did not progress or die will be censored at the last disease evaluation date. For participants who receive subsequent antimyeloma therapy and have not progressed and are alive before the start of the subsequent therapy, data will be censored at the last disease evaluation before the start of any subsequent antimyeloma therapy.

5.4.3.2. Analysis Methods

Analysis of DOR will be based on participants in the all treated analysis set and in the response-evaluable analysis set who achieve a PR or better response, using disease response based on computerized algorithm and disease response based on investigator's assessment. The distribution of DOR will be estimated using the Kaplan-Meier method. The number and percentage of participants with DOR events or are censored will be included. The median DOR with 95% CI will be provided. The Kaplan-Meier curve for DOR will be provided.

5.4.4. Progression-free Survival

5.4.4.1. Definition

Progression-free survival is defined as the time from the date of the first infusion of cilta-cel OOS to the date of first documented disease progression, as defined in the IMWG criteria[4], or death due to any cause, whichever occurs first.

Determinations of dates of PFS event and dates for censoring are summarized in Table 2 as follows.

Table 2: PFS Event and Censoring Method

Situation	Outcome	Date of Event or Censoring
Disease progression prior to start of subsequent antimyeloma therapy	PFS event	Earliest date that indicates disease progression
Death (without prior documented progressive disease or start of subsequent antimyeloma therapy)	PFS event	Date of death
No post-baseline disease assessment	Censored	Date of infusion of cilta-cel OOS
Other (prior to disease progression or death), such as: • Withdrawal of consent to study participation • Lost to follow-up • Start of subsequent antimyeloma therapy	Censored	Date of last disease assessment prior to: • Withdrawal of consent to study participation • Lost to follow-up • Start of subsequent antimyeloma therapy

5.4.4.2. Analysis Methods

The analysis will be based on the all treated analysis set using PFS based on investigator assessment and PFS based on computerized algorithm according to IMWG criteria. The distribution of PFS will be estimated using the Kaplan-Meier method. The number and percentage of participants with PFS events or are censored will be included. The median PFS with 95% CI will be provided. The Kaplan-Meier curve for PFS will be provided. The reasons for PFS censoring will be summarized.

5.4.5. Overall Survival

5.4.5.1. Definition

Overall survival is defined as the time from the date of the initial infusion of cilta-cel OOS to the date of the participant's death for any reason. Participants who died after consent withdrawal or start of subsequent therapy will be considered as having an OS event. If the participant is alive or the survival status is unknown, then the participant's data will be censored at the date the participant was last known to be alive. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.4.5.2. Analysis Methods

The distribution of OS will be estimated using the Kaplan-Meier method. The number and percentage of participants with OS events or are censored will be included. The median OS with 95% CI will be provided. The Kaplan-Meier curve for OS will be provided.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

See Section 5.7 for definitions and analyses of exploratory endpoints.

5.6. Safety Analyses

All safety analyses will be based on the all treated analysis set, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

5.6.1. Extent of Exposure

The number and percentage of participants in the all consented analysis set who receive study intervention (cilta-cel OOS), cyclophosphamide, and fludarabine, and alternative lymphodepleting chemotherapy infusions will be summarized.

The following exposure summaries will be presented based on the all treated analysis set.

Descriptive statistics for total infused volume of the cilta-cel OOS, duration of cilta-cel OOS infusion, weight-adjusted CAR-positive viable T cells infused ($x10^6$ cells/kg) will be presented. The total dose of the cyclophosphamide and fludarabine infusion (mg/m^2) will be summarized with descriptive statistics.

The number and percentage of participants with a dose adjustment (infusion aborted or interrupted for cilta-cel OOS infusion, infusion aborted for cyclophosphamide and fludarabine infusions) will be summarized. The reasons for dose adjustments (adverse event, other) will also be summarized.

The number and percentage of participants with delay of lymphodepleting chemotherapy and the reasons for delay (adverse event, other) will be summarized. Similar summaries will be provided for participants with delay of cilta-cel OOS infusion.

A summary of the number of participants and percentage in the all treated analysis set whose cilta-cel product is out-of-specs in each commercial and clinical specification will be provided.

Listing of exposure information for cilta-cel OOS, and lymphodepleting regimen including cyclophosphamide, fludarabine and alternative lymphodepleting chemotherapy will be provided. A listing of commercial and clinical specifications that the cilta-cel OOS administered did not meet will be included.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the latest version of the MedDRA dictionary. AE severity will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, with the exception of (1) Cytokine Release Syndrome (CRS) and Immune effector Cell-associated Neurotoxicity (ICANS), which will be evaluated according to the ASTCT[3] consensus grading system (protocol section 10.7, Appendix 7, and protocol section 10.8, Appendix 8), and (2) AEs associated with changes in handwriting, which will be graded according to the Handwriting Adverse Event Toxicity Grading Criteria in protocol section 10.12, Appendix 12.

Treatment-emergent adverse events (TEAEs) are defined as any AE that occurs on or after the start of cilta-cel OOS infusion through 100 days after the cilta-cel OOS infusion or the start of subsequent anti-myeloma therapy, whichever is earlier; or any AE that is considered related to

study intervention regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered related to study intervention by the investigator. If the event occurs on the day of the initial administration of study intervention, the event will be assumed to be treatment emergent. If the event onset date is recorded as partial or completely missing, then the event will be considered treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date.

For each type of adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized. Unless otherwise specified, at each level (e.g., system organ class [SOC] and/or preferred term [PT]) of participant summarization in reporting the incidence of an AE, a participant is counted once if one or more events were recorded. Summary tables will be sorted by descending order of frequency.

The following summary tables will be provided for treatment-emergent adverse events:

- An overview of TEAEs, including number of participants with TEAEs, treatment-emergent SAEs, TEAEs related to study intervention, treatment-emergent SAEs related to study intervention, TEAEs of maximum grade of 1 to 5, TEAEs with outcome of death, TEAEs with outcome of death that are related to study intervention.
- TEAEs by SOC, PT, and relationship to study intervention
- TEAEs by SOC, PT and worst toxicity grade 3 or higher
- Most common (frequency of ≥10% in total) TEAEs by SOC, PT, and worst toxicity grade 3 or higher
- TEAEs by SOC, PT, and worst toxicity grade
- Toxicity grade 3 or 4 TEAEs by SOC and PT
- Toxicity grade 3 or 4 TEAEs by SOC, PT, and relationship to study intervention
- Treatment-emergent SAEs by SOC and PT
- Treatment-emergent SAEs by SOC, PT, and relationship to study intervention
- Treatment-emergent SAEs by SOC, PT, and worst toxicity grade 3 or higher
- TEAEs with outcome of death by SOC, PT and relationship to study intervention

In addition, AEs that occur on or after cilta-cel OOS infusion date by SOC, PT, and worst toxicity grade 3 or higher will be summarized. Overall summaries of treatment-emergent COVID-19 adverse events and COVID-19 AEs with onset on or after cilta-cel OOS infusion date will be provided.

In addition, AE listings will be provided for:

- TEAEs with toxicity grade 3 or higher
- treatment-emergent serious AEs

- TEAEs with outcome of death
- AEs leading to withdrawal, interruption or dose reduction of any study drug (cilta-cel OOS, cyclophosphamide, fludarabine) defined as AEs with "Drug withdrawn", "Drug Interrupted", or "Dose reduced" as reported action taken with cilta-cel OOS, cyclophosphamide or fludarabine on CRF page "Adverse Events'/Serious AEs"
- COVID-19 AEs of grade 3 or higher
- AEs that occur on or after the administration start date of the lymphodepleting chemotherapies and before cilta-cel OOS infusion date

A summary of deaths and primary cause of deaths will be presented. A listing of participants who died will be provided. The listing will include date of death, study day of death and relevant details about the deaths that are collected in the eCRF.

5.6.3. Adverse Events of Special Interest

Adverse events of special interest will be summarized as specified below. See Appendix 8 Adverse Events of Special Interest for list of adverse events in each category.

5.6.3.1. Cytokine Release Syndrome (CRS)

For treatment-emergent CRS events, a summary of maximum toxicity grade of CRS events (according to ASTCT consensus grading system), the time from initial cilta-cel OOS infusion to first onset of CRS, the duration of CRS in days, the outcome of CRS, and the treatment measures for CRS will be provided.

In addition, treatment-emergent symptoms of CRS will be summarized by MedDRA SOC, PT and maximum toxicity grade.

A listing will be provided respectively for participants who had any treatment-emergent symptoms of CRS, and for participants who had any serious treatment-emergent symptoms of CRS.

5.6.3.2. Neurological Adverse Events

Neurological adverse events include CAR-T cell neurotoxicity (ICANS, other neurotoxicities) and other neurologic adverse events. CAR-T cell neurotoxicity are defined as AEs marked as AESI category 'Neurotoxicity' and deemed related to cilta-cel OOS by investigators on the CRF page 'Adverse Events/Serious AEs'. Other neurotoxicities are defined as AEs that are reported as CAR-T cell neurotoxicity that are neither ICANS nor the associated symptoms of ICANS.

CAR-T cell neurotoxicity (ICANS, other neurotoxicities)

CAR-T cell neurotoxicity with onset after cilta-cel OOS infusion will be summarized by MedDRA SOC, HLGT, HLT, PT, and worst toxicity grade (by All Grades, Grade 3 or 4, and Grade 5). The summary will include summaries for ICANS and other neurotoxicities separately as well as for the two categories combined.

For treatment-emergent ICANS, the maximum toxicity grade of ICANs (according to ASTCT consensus grading system), the time from cilta-cel OOS infusion to first onset of ICANS, the duration of ICANS in days, the outcome of ICANS, the treatment of ICANS, and concurrent CRS will be summarized as well. A similar summary of ICANS following cilta-cel OOS infusion will be provided. A shift table from baseline to worst Immune-Effector Cell-Associated Encephalopathy (ICE) scores during the post infusion period will be provided.

In addition, treatment-emergent symptoms of ICANS by MedDRA SOC, PT and worst toxicity grade will be summarized. A listing of serious treatment-emergent symptoms of ICANS will be provided.

For other neurotoxicities after cilta-cel OOS infusion, the maximum toxicity grade, the time from initial cilta-cel OOS infusion to first onset of other neurotoxicities, the duration of other neurotoxicities in days, and the outcome of other neurotoxicities will be summarized. The following listings will be provided:

- ICANS on or after cilta-cel OOS infusion date
- other neurotoxicities on or after cilta-cel OOS infusion date

Other neurologic adverse events

Other neurologic adverse events with onset after cilta-cel OOS infusion, i.e., AEs with primary system organ class of "Nervous system disorders" or "Psychiatric disorders" that are not identified as AESI ‘Neurotoxicity’ related to cilta-cel OOS by investigators, will be summarized by MedDRA SOC, High Level Group Term (HLGT), High Level Term (HLT), PT, and relationship to study intervention, and by worst toxicity grade (by All Grades, Grade 3 or higher).

In addition, a listing will also be provided for other neurologic adverse events observed after cilta-cel OOS infusion.

5.6.3.3. Prolonged and Recurrent Cytopenias

For definition of prolonged or recurrent cytopenias, see Appendix 8 Adverse Events of Special Interest. Incidences of prolonged or recurrent cytopenias following treatment with cilta-cel OOS will be summarized with count and percentage.

5.6.3.4. Secondary Primary Malignancies

Secondary primary malignancies will be summarized by preferred term and by clinically-reviewed categories (cutaneous/non-invasive, non-cutaneous/invasive, or hematologic malignancies). If the number of incidences of second primary malignancies is small, this summary will be replaced by the listing described below.

A listing of participants who reported other malignancies (including second primary malignancies) during the study will be provided.

5.6.4. Other Adverse Events

Treatment-emergent cytopenias by MedDRA SOC, PT and worst toxicity grade (All Grades, Grade 3 or 4, and Grade 5), hypogammaglobulinemia by SOC and PT, hypersensitivity reactions (including infusion-related reactions) by SOC, PT and relationship to study intervention, and infections (including the HBV reactivation) by SOC, HLGT, PT, and worst toxicity (by All grades, Grade 3 or 4, and Grade 5) will be summarized. A summary of infection AEs with onset on or after cilta-cel OOS infusion by SOC, HLGT, PT, and worst toxicity (by All grades, Grade 3 or 4, and Grade 5) may be provided. In addition, a summary of cranial nerve palsy with onset on or after cilta-cel OOS infusion date and a summary of peripheral neuropathies with onset on or after cilta-cel OOS infusion date similar to the summary of ICANS will be provided, i.e. including summaries of maximum toxicity grade, time to first onset, time to recovery, duration and outcome of the cranial nerve palsy (peripheral neuropathies).

Corresponding listings for these AEs (a listing of treatment-emergent HBV DNA positive and HBV infection serious adverse event for the all treated analysis set, a listing of treatment-emergent hypersensitivity reactions (including infusion-related reactions) for the all treated analysis set, and a listing of fever, and/or hypotension, and/or hypoxia within 60 days of cilta-cel OOS infusion for participants in the all treated analysis set without CRS) will be provided. Movement and neurocognitive AEs following cilta-cel OOS infusion will be listed for the all treated analysis set. The following listings may be provided for the all treated analysis set for these AEs with onset after cilta-cel OOS infusion: peripheral neuropathies, cranial nerve palsies, autoimmune disorders, and Guillain-Barré Syndrome.

These AEs mentioned above are defined in the table below.

Table 3 – Definitions for Other AEs

AE Category	Subcategory	Preferred Term and Other Criteria
Other AEs	Hypersensitivity reactions	Hypersensitivity reactions (SMQ-Narrow). (a) Limit to within 24 hours of infusion: AE start date – cilta-cel OOS start date +1 <= 2 or (b) the AE record is marked as infusion reaction associated with cilta-cel OOS in CRF page “Adverse Events/Serious AEs”
Other AEs	Cytopenias	Preferred Term is "Neutropenia", "Thrombocytopenia", "Anaemia", "Leukopenia", or "Lymphopenia"
Other AEs	Hypogammaglobulinemia	Preferred Term is “Hypogammaglobulinaemia”
Other AEs	Infections	Coded body system is “Infections and infestations”
Other AEs	HBV Infection	Pathogen name (case-insensitive) entered in CRF page “Adverse Events/Serious AEs” for an infection serious adverse event is 'HBV' or 'HEPATITIS B VIRUS'
Other AEs	HBV DNA Positive	If HBV infections (as defined above) and lab result on CRF page ‘Serology’ for HBV DNA is positive
Other AEs	fever, and/or hypotension, and/or hypoxia	Preferred Term (case-insensitive) is "PYREXIA", "HYPOTENSION", "HYPOXIA", "FEBRILE NEUTROPENIA", or "NEUTROPENIC FEVER"

Other AEs	Peripheral Neuropathy	High level group term (case-insensitive) is 'PERIPHERAL NEUROPATHIES'
Other AEs	Cranial Nerve Palsy	AEs that satisfy one of the following conditions (all text searches are case-insensitive): (a) High level group term is 'CRANIAL NERVE DISORDERS (EXCL NEOPLASMS)' and preferred term is not in this list: 'ANOSMIA', 'PAROSMIA', ''NUMB CHIN SYNDROME', 'OLFACTORY DYSFUNCTION', 'HYPOSMIA', 'ACCESSORY NERVE DISORDER'; (b) High level group term is 'INNER EAR AND VIIITH CRANIAL NERVE DISORDERS' and preferred term is not in this list: 'TINNITUS', 'VERTIGO'
Other AEs	Guillain-Barré Syndrome	Preferred term (case-insensitive) is one of the following: 'demyelinating polyneuropathy', 'guillain-barre syndrome'
Other AEs	movement and neurocognitive AEs	AE is marked as AESI of category 'Neurotoxicity' and related to cilta-cel OOS on CRF page 'Adverse Events' and have an onset more than 14 days after cilta-cel infusion for participants who had no CRS/ICANS events OR with onset after the recovery of ICANS and/or CRS period (i.e. more than 14 days after the end date of last CRS/ICANS) for participant who had CRS/ICANS events and preferred term (case-insensitive) falls in one of the following: (1) Movement disorder: preferred term is 'Agraphia', 'Ataxia', 'Balance disorder', 'Bradykinesia', 'Cogwheel rigidity', 'Coordination abnormal', 'Dysgraphia', 'Dyskinesia', 'Dysmetria', 'Essential tremor', 'Extrapyramidal disorder', 'Gait disturbance', 'Hand-eye coordination impaired', 'Head titubation', 'Micrographia', 'Motor dysfunction', 'Myoclonus', 'Parkinsonism', 'Posture abnormal', 'Resting tremor', 'Stereotypy', 'Tremor'; (2) Cognitive disorder: preferred term is 'Amnesia', 'Apraxia', 'Bradyphrenia', 'Cognitive disorder', 'Confusional state', 'Depressed level of consciousness', 'Disturbance in attention', 'Encephalopathy', 'Incoherent', 'Leukoencephalopathy', 'Lack of consciousness', 'Loss of consciousness', 'Memory impairment', 'Mental impairment', 'Mental status changes', 'Noninfective encephalitis', 'Psychomotor retardation', 'Mental disorder'; (3) Personality changes: preferred term is 'Affect lability', 'Apathy', 'Flat affect', 'Indifference', Personality change', 'Reduced facial expression'
Other AEs	autoimmune disorders	identified through clinical review of AEs

5.6.5. Additional Safety Assessments

5.6.5.1. Clinical Laboratory Tests

Clinical laboratory tests (hematology, coagulation, chemistry, quantitative immunoglobulin) will be analyzed for the all treated analysis set as specified below.

Descriptive statistics will be presented for selected chemistry and hematology laboratory tests at scheduled time points. Change from baseline will be summarized with descriptive statistics for chemistry and hematology tests. The worst toxicity grade in hematology, coagulation, and chemistry after cilta-cel OOS infusion will be summarized by toxicity grade. Shift tables from baseline to worst toxicity grade during the post-infusion period will be provided for selected laboratory analytes.

Listings of laboratory results outside of reference range will be provided. A listing of ferritin values greater than > 500 μg/L will be provided.

5.6.5.2. Vital Signs and Physical Examination Findings

Vital sign parameters include temperature, pulse, blood pressure (systolic and diastolic), and oxygen saturation (%). Vital sign measurements and change from baseline will be summarized at each scheduled assessment time point.

Treatment-emergent vital sign results are defined as results on or after the date (and time as applicable) of the cilta-cel OOS infusion. Incidence of treatment-emergent clinically important abnormal vital signs, as defined in Table 4, will be summarized for participants who had a baseline assessment and at least 1 post-baseline assessment for that vital sign. A listing of participants with treatment-emergent clinically important abnormalities in vital signs will be presented.

Table 4: Clinically Important Abnormal Vital Signs

Vital Sign	Criteria
Pulse	>110 bpm and with >20 bpm increase from baseline
	<50 bpm and with >15 bpm decrease from baseline
Systolic blood pressure	>180 mm Hg and with >20 mm Hg increase from baseline
	<90 mm Hg and with >20 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >15 mm Hg increase from baseline
	<50 mm Hg and with >15 mm Hg decrease from baseline
Temperature	>38°C and with ≥1°C increase from baseline
Respiratory rate	>20 or <7 breaths per minute
Oxygen saturation	<95%

5.6.5.3. Cardiac Function Assessments

For MUGA scan (optional), a listing will be provided.

5.6.5.4. ECOG Performance Score

ECOG performance status evaluates the effect of the disease status on the activities of daily living. Descriptive statistics will be used to summarize ECOG performance status at baseline and scheduled post-baseline timepoints during the post-infusion period. Shift table from baseline to post-baseline scheduled visit and to worst score during the post-infusion period (Day 100 + 14 days window) will be provided. In addition, a listing of ECOG scores may be provided.

5.7. Other Analyses

5.7.1. Pharmacokinetics

PK analyses will be performed on the PK analysis set and will be described in a separate analysis plan.

5.7.2. Immunogenicity

5.7.2.1. Immunogenicity Analysis

Immunogenicity analyses will be described in a separate analysis plan.

5.7.3. Pharmacodynamics

Pharmacodynamic analyses, if performed, will be described in a separate analysis plan.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic/pharmacodynamic modeling may be performed. If performed, details and results of the analysis will be presented in a separate report.

5.7.5. Biomarkers

Biomarker analyses are designed to identify markers predictive of response (or resistance) to cilta-cel OOS. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information. Results of biomarker analyses may be presented in a separate report.

5.7.5.1. Minimal Residual Disease (MRD)

5.7.5.1.1. Analysis Methods

Details on MRD negativity analyses are described in Section 5.4.2.

5.7.5.2. Replication competent lentivirus (RCL)

Whole blood from participants treated with cilta-cel OOS will be evaluated for the presence of lentiviral vesicular stomatitis virus-G using a qPCR assay.

5.7.5.2.1. Analysis Methods

The number and percentage of participants in the all treated analysis set with incidence of replication competent lentivirus (RCL) detected in blood samples will be summarized. A summary of reasons for missing RCL results will be provided if the data are available.

5.7.5.3. Molecular Subtyping

5.7.5.3.1. Molecular Subtypes

Bone marrow aspirate samples may be assessed for specific molecular subtypes having chromosomal aberrations such as del17p, t(4;14), t(14;16), and gain/amp1q.

5.7.5.3.2. Molecular Risk Subgroup Analysis

Cytogenetic high-risk is defined as participants with any of the molecular subtypes del17p, t(14;16), and t(4;14) at baseline. Cytogenetic standard-risk is defined as participants without any of the molecular subtypes del17p, t(14;16), and t(4;14) at baseline. If results of all three molecular subtypes del17p, t(14;16), and t(4;14) at baseline are missing, cytogenetic risk is considered to be unknown.

A different definition of high-risk molecular subgroup, called revised cytogenetic high-risk (defined as presence of any of the molecular subtypes del17p, t(14;16), t(4;14), and gain/amp1q at baseline), will also be used. Revised cytogenetic standard-risk is defined as participants without any of the molecular subtypes del17p, t(14;16), t(4;14), and gain/amp1q at baseline. If results of all molecular subtypes del17p, t(14;16), t(4;14), and gain/amp1q at baseline are missing, revised cytogenetic risk is considered to be unknown. To determine if cilta-cel OOS will lead to improved clinical responses in standard-risk as well as high-risk molecular subgroups, cytogenetic subgroup analyses are specified in Section 5.7.7.

5.7.5.4. Cytokine profiling

Graphs of cytokines (mean (+/-SD) and median) over time may be generated. Additionally, exploratory analyses summarizing cytokines (C_{max} and exposure ($AUC_{0\text{-}56d}$)) grouped by response categories (responder [PR or better] vs. non-responder, CR/sCR vs. non-CR/sCR), by worst CRS toxicity grade, or by CAR-T cell neurotoxicity (ICANS and Other Neurotoxicities) might be generated.

5.7.5.5. Immunophenotyping

Immune cell populations (including CAR-T cells) in peripheral blood and malignant plasma cells in bone marrow from participants will be evaluated for expression of several markers including but not limited to immune-specific markers (CD4+, CD8+, etc.) and tumor associated markers (such as BCMA). Baseline BCMA samples were not collected.

Graphs of CD4+CAR+/CD8+CAR+ T cell ratio grouped by response categories (responder [PR or better] vs. non-responder, CR/sCR vs. non-CR/sCR), by worst CRS toxicity grade, or by CAR-T cell neurotoxicity (ICANS and Other neurotoxicities) might be generated.

5.7.6. Analyses for COVID-19

Analyses for COVID-19 are described in Sections 5.6.2, 6.4, 6.5.3, and 6.6, i.e. including an overall summary of treatment-emergent COVID-19 AEs, an overall summary of COVID-19 AEs with onset on or after cilta-cel OOS infusion date, a listing of COVID-19 AEs of grade 3 or higher, a listing of minor protocol deviations due to COVID-19, a summary of concomitant medications used for COVID-19 AEs by preferred ATC class and drug name, and a summary and listing of COVID-19 medical history.

5.7.7. Subgroup Analyses

5.7.7.1. Definition of Subgroups

See Table 5 for definitions.

5.7.7.2. Analyses

In general, subgroup analyses on the pre-specified subgroups in the all treated analysis set in Table 5 below will be performed for the primary efficacy endpoint ORR and PFS by computerized algorithm and by investigator assessment (efficacy analysis type (E) in Table 5). Additionally, for ORR, these subgroup analyses will also be performed for the response-evaluable analysis set. The overall summaries of TEAEs will be generated for subgroups with safety analysis type (S) in Table 5 for the all treated analysis set.

Table 5: Subgroup Analyses

Subgroup	Definition	Analysis Type
Clinical specifications [a]	• Met all clinical specifications • Did not meet at least one clinical specification	E, S
Met commercial specification for post-thaw viability of cilta-cel product [a]	• Yes • No o Met clinical specification o Did not meet clinical specification	E, S
Met commercial specification for vector copy number per transduced cell of cilta-cel product [a]	• Yes • No o Met clinical specification o Did not meet clinical specification	E, S
Met commercial specification for CAR+ Viable T cells/kg in final container of cilta-cel product [a]	• Yes • No o Met clinical specification o Did not meet clinical specification	E, S
Met commercial specification for CAR expression from viable T cells of cilta-cel product [a]	• Yes • No o Met clinical specification o Did not meet clinical specification	E, S
Number of lines of prior therapy	• ≤6 • >6	E
Cytogenetic risk [b]	• High-risk • Standard risk	E
Revised cytogenetic risk [c]	• High-risk • Standard-risk	E
≥ 2 revised high-risk cytogenetic features [d]	• Yes • No	E
Presence of extramedullary plasmacytomas subgroup	• Yes • No	E
Plasmacytosis [e]	• Yes • No	E, S
Triple class refractory disease [f]	• Yes • No	E
< 6 months to PD from start of last prior systemic therapy [g]	• Yes • No	E

< 18 months to PD from start of last prior ASCT [h]	• Yes • No	E
High-risk (based on comorbidity) [i]	• Yes • No	E, S
Age group	• < 65 years • ≥ 65 years	E, S
ECOG at baseline	• 0 • 1 • ≥ 2	E
Received prior BCMA therapy	• Yes • No	E
Informed consent within 6 month of CARVYKTI approval [j]	• Yes • No	E
Received alternative lymphodepleting chemotherapy [k]	• Yes • No	E, S

Key: ASCT= autologous stem cell transplant, BCMA = B-cell maturation antigen, E = efficacy, PD = progressive disease, S = safety

[a] Clinical and commercial specifications at the time of CARVYKTI approval.
[b] High-risk is defined as abnormal in del17p, t(4;14) or t(14;16). Standard risk is not high-risk and had at least one normal cytogenetic testing result for the del17p, t(4:14), or t(14:16).
[c] High-risk is defined as abnormal in del17p, t(4;14), t(14;16), or gain/amp1q. Standard risk is not high-risk and had at least one normal cytogenetic testing result for the del17p, t(4:14), t(14:16), or gain/amp1q.
[d] Participant had at least 2 of the following abnormalities: del17p, t(4;14), t(14;16), or gain/amp1q
[e] Maximum of baseline plasma cells by aspirate and by biopsy ≥ 60%
[f] Participant with refractory to prior PI and anti-CD38 and IMiD
[g] Participants who progressed on the last prior systemic therapy less than 6 months from start of the last prior systemic therapy
[h] Participants who progressed on the last prior ASCT less than 18 months from the start of the last prior ASCT
[i] High-risk (based on comorbidity) is defined as meeting at least one of the following criteria: (1) having coded medical history/event from CRF page 'General Medical History' flagged by clinical review as prior malignancy, cardiac, autoimmune disease, (2) having history of stroke/CVA/ischemic stroke/transient ischemic attack from clinical review of coded medical history/event from CRF page "General Medical History" or if participant had a history of stroke from entry in CRF page "Neurologic History", (3) revised International Staging System (ISS) at initial diagnosis is III, or (4) renal impairment (creatinine clearance at screening < 40 mL/min/1.73 m^2).
[j] informed consent date is before or on August 31, 2022
[k] Participants who did not receive both fludarabine and cyclophosphamide as lymphodepleting chemotherapy

5.8. Interim Analyses

No formal interim analysis is planned for the study.

A Data Review Committee (DRC) was established as detailed below to monitor safety. Analyses for DRC's review are described in a separate DRC SAP.

5.8.1. Data Review Committee (DRC)

The DRC includes sponsor personnel independent of the study team, at least one medical expert with expertise and clinical experience in the diagnosis and management of multiple myeloma, and at least one statistician. The membership, responsibilities, frequencies of planned meetings, and process and convention of the DRC are described in a separate DRC charter.

The DRC members perform periodic independent reviews, and if necessary, unscheduled reviews of study data. After each review, the DRC make recommendations regarding the continuation of the study as well as any modifications of the study. Initially, data were to be reviewed by the DRC

after every 10 participants have been treated and followed for at least 3 months. There were 3 DRC meetings conducted: DRC1 when there were around 20 participants who completed Day 56 visit, DRC2 when 49 participants completed Day 56 visit, and DRC3 meeting after enrollment ended. The timing of DRC was changed slightly from the original timing specified in the protocol due to quick enrollment and for DRC1, to allow for sufficient efficacy data collection for DRC committee's review.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADA	anti-drug antibody
AE	adverse event
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
BCMA	B-cell maturation antigen
BSA	body surface area
CAR-T	Chimeric antigen receptor T (cells)
CI	confidence interval
cilta-cel	ciltacabtagene autoleucel
C_{max}	maximum concentration
CBR	clinical benefit rate
COVID-19	Coronavirus Disease 2019
CR	complete response
CRS	cytokine release syndrome
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
DOR	duration of response
DRC	Data Review Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End of Study
FLC	free light chain
HLGT	high level group term
HLT	high level term
ICANS	Immune effector cell-associated neurotoxicity
ICE	Immune-effector cell-associated encephalopathy
IMWG	International Myeloma Working Group
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OOS	out-of-specifications
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
qPCR	quantitative polymerase chain reaction
RCL	replication competent lentivirus
SAE	serious adverse event
SAP	Statistical Analysis Plan
sBCMA	soluble B-cell maturation antigen
sCR	stringent complete response
SD	standard deviation
SMQ	standardized MedDRA query
SOC	system organ class
SPEP	serum protein electrophoresis
SIFE	serum immunofixation

TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
UPEP	urine protein electrophoresis
UIFE	urine immunofixation
USPI	United States prescribing information
VGPR	very good partial response
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

There are no changes to protocol-planned analyses.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in the all treated analysis set will be presented.

Table 6 presents a list of the demographic variables that will be summarized for the all treated analysis set.

Table 6: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Surface Area (BSA) (m^2)	
Categorical Variables	
Age (<65 years, 65-75 years, >75 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated, unknown)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not reported, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported)	
Baseline ECOG score	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 7 presents a list of the baseline disease characteristics variables that will be summarized for all treated analysis set.

Table 7: Baseline Disease Characteristics Variables

Continuous Variables	**Summary Type**
Time since initial multiple myeloma diagnosis (years), defined as cilta-cel infusion start date – date of initial multiple myeloma diagnosis + 1, divided by 365.25	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Categorical Variables	
Type of multiple myeloma (IgG, IgA, IgM, IgD, IgE, free light chain only, biclonal, or negative immunofixation)	Frequency distribution with the number and percentage of participants in each category.
Type of measurable disease (Serum only, Serum and urine, Urine only, or Serum FLC)	
Number of lytic bone lesions (None, 1-3, 4-10, more than 10)	
Presence of extramedullary plasmacytomas (Yes, No)	
Bone marrow % plasma cells (<10, 10-30, >30-<60, ≥60) by biopsy or aspirate	
Bone marrow cellularity (hypercellular, normocellular, hypocellular, indeterminate) by biopsy or aspirate	
High-risk cytogenetic abnormalities (del17p, t(4;14), or t(14;16))	
Cytogenetic standard risk (participants with cytogenetic test results and do not have del17p, t(4;14) or t(14;16)	
Revised high-risk cytogenetic abnormalities (del17p, t(4;14), t(14;16), or gain1q/amp1q)	
Revised cytogenetic standard risk (participants with cytogenetic test results and do not have del17p, t(4;14), t(14;16) or gain1q/amp1q)	

Listings of demographic and baseline disease characteristics will be provided for the all treated analysis set.

As a reference to the patient population in CARTITUDE-1, a table summarizing count and percentage of participants in the all treated analysis set with the following baseline

characteristics listed in Table 8 which result in participants would not have met the CARTITUDE-1 key inclusion/exclusion criteria will be provided

Table 8: Baseline Characteristics Not Meeting the CARTITUDE-1 Key Inclusion/Exclusion Criteria

Baseline Characteristics
Any grade 3-4 baseline cytopenia: • Hemoglobin < 8 g/dL • Platelets < 50,000/µL • Absolute neutrophils count (ANC) <0.75×10^9/L • Lymphocyte count < 0.3 x 10^9/L
Prior anti-BCMA therapy: • Belantamab mafodotin • BCMA-directed CAR-T cell therapy • Other anti-BCMA therapies
History of allogenic stem cell transplant
Organ dysfunction • Renal impairment (creatinine clearance < 40 mL/min/1.73 m^2) • Liver impairment (total bilirubin > 2.0 × ULN) • Impaired cardiac function (LVEF < 45%)
Disease characteristics: rare subtypes (PCL, amyloidosis, POEMS)
Other: • Baseline ECOG performance status ≥2 • History of prior malignancies • Corrected calcium > 12.5 mg/dL • AST or ALT > 3.0 × upper limit of normal (ULN) • On chronic immunosuppressive therapy
With no criteria above
With 1 criterion above
With >1 criterion above

6.4. Appendix 4 Protocol Deviations

Participants with major protocol deviations will be identified prior to database lock. Participants with major protocol deviations will be summarized by category for the all treated analysis set. A summary of minor protocol deviations due to COVID-19 will be generated if there is a large number of these deviations.

A listing of all major protocol deviations will be provided for the all consented analysis set. A listing of minor protocol deviations due to COVID-19 will be provided.

6.5. Appendix 5 Prior, Concomitant and Follow-Up Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention (cilta-cel OOS) infusion. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

6.5.1. Prior Exposure to Multiple Myeloma Therapies

A summary of prior exposure to multiple myeloma therapies (systemic therapy, stem cell transplant, radiotherapy, or cancer-related surgery/procedure) will be provided. Specifically, the number of prior lines of therapy will be summarized with descriptive statistics and summarized by grouped categories, such as <3, 3, and >3 with frequencies. A summary of prior systemic therapies by therapeutic class, pharmacologic class, and drug name will be provided.

Additionally, the summary of prior systemic therapies will be presented by therapy class and therapy. The therapy classes include proteasome inhibitors (PI), immunomodulatory drugs (IMiD), anti-CD38 antibody, steroids, alkylating agents and anthracyclines. Therapies included in the PI class are: bortezomib, carfilzomib, oprozomib, marizomib, and ixazomib; IMiD class: lenalidomide, pomalidomide, and thalidomide; anti-CD38 antibody class: daratumumab, and isatuximab; monoclonal antibody class: elotuzumab; and steroids class: dexamethasone and prednisone, among others.

The number of participants who had prior exposure to multiple therapy classes (e.g., PI + IMiD) may be provided, if the number of participants who exposed to those therapy classes is sufficient.

6.5.2. Refractory Disease

Refractory is defined as being nonresponsive (either failure to achieve minimal response or development of progressive disease) while on therapy or progressed within 60 days of the therapy's end date.

For each participant, refractory status (yes, no) to a particular prior multiple myeloma therapy class (e.g., PI/IMiD) or prior multiple myeloma therapy (e.g., bortezomib or thalidomide) refers to refractory to any prior therapy-containing line.

The number and percentage of participants' refractory status to PI, IMiD, or anti-CD38 antibody therapy class will be summarized by the following categories: any PI, any IMiD, any anti-CD38 antibody, both PI and IMiD, both anti-CD38 and IMiD, both PI and anti-CD38 antibody, PI and anti-CD38 and IMiD (triple refractory), and at least 2 PIs and at least 2 IMiDs and 1 anti-CD38 antibody (penta refractory). Refractory to specific prior multiple myeloma therapy, such as bortezomib, carfilzomib, ixazomib, lenalidomide, pomalidomide, thalidomide, daratumumab or isatuximab, elotuzumab and the relevant combinations of the aforementioned therapies, will be provided.

The incidence of participants who are refractory to any prior line, and who are refractory to their last line of therapy will be reported.

A listing of prior systemic therapies may be provided.

6.5.3. Concomitant Medications

Summaries of concomitant medications will be presented by ATC term. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

In addition, concomitant medications of special interest will be presented. These include medications given for CRS and symptoms of CRS, for cilta-cel OOS-related neurotoxicity and symptoms of cilta-cel OOS-related neurotoxicity, medications given for ICANS and symptoms of ICANS, as well as use of intravenous immunoglobulin (IVIG), prophylactic antimicrobial medications (antiviral prophylactic, antibacterial prophylactic, antifungal prophylactic), growth factor, and systemic steroids. See Appendix 9 for list of medications in each category. Pre-infusion medications, bridging therapy, and therapeutic/surgical procedures will be summarized.

A summary of concomitant medications used for COVID-19 AEs by preferred ATC class and drug name will be provided. Transfusions and oxygen supplementation will be summarized as well. Oxygen supplementation summary will include frequencies and percentages of types of oxygen delivery method and positive pressure.

6.5.4. Subsequent Antimyeloma Therapy

The total number of participants in the all treated analysis set who received subsequent antimyeloma therapy will be reported. A summary of subsequent antimyeloma therapy for the all treated analysis set will be presented by therapeutic class, pharmacologic class, and drug name, coded using the WHO-DD. In addition, for participants who received subsequent antimyeloma therapy, their best response to the first subsequent antimyeloma therapy will be summarized.

Time to subsequent antimyeloma treatment is defined as the time from the start date of cilta-cel OOS infusion to the start date of subsequent antimyeloma treatment. Death due to progressive disease without the start of any subsequent therapy will be considered as event. For censored participants, participants who die due to causes other than progressive disease will be censored at the date of death; others will be censored at the last date known to be alive. The distribution of time to subsequent therapy will be estimated using the Kaplan-Meier method. The median time to subsequent therapy with 95% CI will be provided. In addition, the number and percentage of participants who had a subsequent therapy event or were censored will be reported. The Kaplan-Meier curve for time to subsequent therapy will be provided.

6.6. Appendix 6 Medical History

Medical history data will be summarized by MedDRA system organ class and preferred term. Neurological history data will be summarized by MedDRA system organ class and preferred term, and for those ongoing at study entry, also by toxicity grade. COVID-19 medical history data may be summarized and listed.

6.7. Appendix 7 Treatment Compliance

Not applicable since cilta-cel OOS is scheduled to be administer via a single infusion.

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE Special Interest Category	Subcategory	Preferred Term and Other Criteria
Cytokine Release Syndrome (CRS)		Preferred Term is “Cytokine release syndrome” and marked as AESI category “Cytokine Release Syndrome” in CRF page “Adverse Events/Serious AEs’
Symptoms of CRS		Preferred Term is not “Cytokine release syndrome” and marked as AESI category “Cytokine Release Syndrome” in CRF page “Adverse Events/Serious AEs’
ICANS		Preferred Term is “CAR T-cell-related encephalopathy syndrome”, or preferred term (case-insensitive) contains ‘IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME’, or verbatim term (case-insensitive) contains ’ICANS’, or verbatim term (case-insensitive) contains ‘IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY SYNDROME’
Symptom of ICANS		marked as “Neurotoxicity” in CRF page “Adverse Events/Serious AEs”, are related to cilta-cel OOS, and with duration overlapping event identified in ICANS above
Other Neurotoxicities		marked as “Neurotoxicity” in CRF page “Adverse Events/Serious AEs”, are related to cilta-cel OOS, and are not ICANS nor symptom of ICANS.
Other Neurologic Adverse Event		primary system organ class equals “Nervous system disorders” or “Psychiatric disorders”, and not marked as “Neurotoxicity” in CRF page “Adverse Events/Serious AEs”
Prolonged or recurrent cytopenias		Lab results (graded according to CTCAE v5.0 grading criteria of "Neutropenia", "Thrombocytopenia", "Anaemia", "Leukopenia", and "Lymphopenia") with initial grade 3 or 4 during the first 100 days after cilta-cel OOS infusion that satisfy at least one of the following criteria: (a) Initial Grade 3 or 4 not recovered to <= Grade 2 by Day 30 (b) Initial Grade 3 or 4 not recovered to <= Grade 2 by Day 60 (c) Grade 3 or 4 after Day 60 after initial recovery of Grade 3 or 4 within 40 days) For (a), (b) and (c), for recovery determination, the lab result with the worst toxicity grade will be used for a calendar day. If the recovery period <=10 days, participants must have consecutive Grade <=2 results from separate days to be considered recovery.
Secondary primary malignancies		Marked as “Second Primary Malignancy” in CRF page “Other Malignancies”

6.9. Appendix 9 Medications of Special Interest

Concomitant medications of special interest are defined as follows:

Concomitant Medication Special Interest Category	**Standard Medication Name and/or Other Criteria**
Antiviral prophylactic	Indication in CRF page 'Concomitant Therapy is 'Prophylaxis' and High Level Group Term (case-insensitive) is "VIRAL INFECTIOUS DISORDERS"
Antibacterial prophylactic	Indication in CRF page 'Concomitant Therapy is 'Prophylaxis' and High Level Group Term (case-insensitive) is "BACTERIAL INFECTIOUS DISORDERS"
Antifungal prophylactic	Indication in CRF page 'Concomitant Therapy is 'Prophylaxis' and High Level Group Term (case-insensitive) is "FUNGAL INFECTIOUS DISORDERS"
Medications given for CRS and Symptoms of CRS	Medications that have indication 'Adverse Event' and the corresponding primary AEs in CRF page "Concomitant Therapy" satisfy the criteria for CRS and/or Symptoms of CRS in Appendix 8 Adverse Events of Special Interest.
Medications given for cilta-cel OOS-related neurotoxicity and symptoms of cilta-cel OOS-related neurotoxicity	Medications that have indication 'Adverse Event' and the corresponding primary AEs in CRF page "Concomitant Therapy" match with the AEs that are marked as 'Neurotoxicity' AESI related to cilta-cel OOS
Medications given for ICANS and symptoms of ICANS	Medications that have indication 'Adverse Event' and the corresponding primary AEs in CRF page "Concomitant Therapy" match with the AEs that are ICANS or symptoms of ICANS (see Appendix 8 Adverse Events of Special Interestfor definition of ICANS and symptoms of ICANS)
Intravenous immunoglobulin (IVIG)	Coded medication class (case-insensitive) contains "IMMUNOGLOBULIN"
Growth factor	CMLVL4CD='L03AA'
Systemic steroid	CMCLASCD='H02AB'

6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Text in gray italic in the below table is present in the grading scale but is not applied by Janssen when grading lab data.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; *bleeding*	-	Clinical signs and symptoms are not taken into consideration for grading.
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal;	>1.5 - 3.0 x ULN if baseline was normal;	>3.0 - 10.0 x ULN if baseline was normal;	>10.0 x ULN if baseline was normal;	Ranges defined for "abnormal baseline" are

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
	> 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x baseline if baseline was abnormal	applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	Ranges defined for "abnormal" are applied only on values < LLN. Grade 0 will be assigned to values > ULN.
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, e.g. grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).
INR increased	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation; bleeding*	-	Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading.
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3;	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
		>4 - 20 x 10e9 /L			
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Metabolism and nutrition disorders					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; *symptomatic*	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *intervention initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium >150 - 155 mmol/L; *intervention initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; *symptomatic*	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*	Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; intervention indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, i.e. worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyponatremia	Sodium <LLN - 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms*	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Worst case ("<130-120 mmol/L" for grade 3

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
			Sodium <130-120 mmol/L		added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used.

* Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.

6.11. Appendix 11 Progressive Disease and Response Algorithm based on IMWG Criteria for Multiple Myeloma

IMWG criteria used for progressive disease and response are outlined in protocol Appendix 10. The detailed computerized algorithm for determining response based on IMWG criteria for multiple myeloma will be outlined in a separate document.

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